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Review Article

Low-Grade Inflammation and Oxidative Stress as Drivers of Obesity-Related Complications: A Narrative Review

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ABSTRACT

Background: The global prevalence of obesity continues to rise, with incidence rates differing markedly between regions. This narrative review synthesizes current evidence on how adipocyte dysfunction connects inflammatory and oxidative pathways to obesity-related complications, particularly cardiometabolic diseases.
Methods: A narrative search of PubMed and Google Scholar was conducted to identify recent publications on the roles of inflammation and oxidative stress in obesity, providing context for the evidence discussed in this review.
Results: The literature reveals that, in obesity, inflammation and oxidative stress are closely related processes originating from adipocyte dysfunction. This dysfunction increases proinflammatory cytokine secretion and triggers inflammatory immune responses. As a result, immune cells in adipose tissue-especially macrophages, but also T cells and neutrophils-adopt proinflammatory phenotypes, contributing to cytokine production and tissue remodeling. Together, impaired immune responses, chronic low-grade inflammation, and oxidative stress disrupt insulin signaling and contribute to metabolic dysfunction.
Conclusion: Adipocyte dysfunction in obesity triggers immune and oxidative stress responses, driving cardiometabolic complications such as insulin resistance, type 2 diabetes, and cardiovascular diseases. Understanding these mechanisms is essential for the development of targeted therapy.

1. Introduction

Obesity has become a global health concern in recent decades. It is associated with various alterations in hormonal, biological, and endothelial levels [1]. The prevalence of obesity is rising even in countries with a history of undernutrition, such as Bangladesh, Nepal, and India. A higher proportion of obesity is now being observed among LMIC (low-middle income countries) populations relative to those from HICs (high-income countries) [2]. Data from the National Health and Nutrition Examination Survey (NHANES) show that between 1980 and 2000, obesity rates increased significantly among adult men (35%) and women (40.4%) in the US [3]. Obesity incidence varies across regions, influenced by factors like socioeconomic status, culture, healthcare access, and environment [4].

Marked variation in obesity prevalence exists both within and between countries. For instance, in 2016, obesity rates among men ranged from 22.7% in Portugal to 29.3% in the UK across 18 European nations [5]. Women's rates similarly fluctuated, from 19.5% in Switzerland to 31.3% in the UK. In Iraq, high rates were reported in both Erbil City and Basrah. Urban obesity rates are now converging with those in rural areas, illustrating how economic growth and changing lifestyles are shifting the patterns of obesity [2].

Obesity rates in the United States show marked regional disparities, with the South and Midwest exhibiting the highest prevalence alongside elevated incidences of diabetes mellitus and metabolic syndrome (MetS) [6]. Globally, much of the increase in body mass index (BMI) stems from rural populations, 55% of the worldwide rise, reaching 80% in some low- and middle-income countries [7]. Data indicate that reduced energy expenditure from work activities correlates with increased weight during the same period. A US population-based study reported that the daily energy expenditure has decreased by more than 100 calories over the last 50 years. This subsequently accounts for a significant increase in mean body weight in the US population, across both genders [8].

Beyond regional variation, dietary patterns and the physical environment play critical roles in obesity's development. High-calorie, low-nutrient diets—often rich in sugars, fats, and processed foods—lead to excessive caloric intake while lacking essential nutrients. When energy expenditure does not match intake, weight gain follows. Unhealthy food options, particularly in low-income areas, drive poor dietary choices due to accessibility and affordability [9]. Ultra-processed foods now comprise 50%-60% of daily energy intake in many high-income nations, paralleling steady increases in overweight and obesity rates over the past century [10].

Other lifestyle factors contribute to obesity risk and its associated health consequences. Poor dietary fat intake, lack of physical

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activity, and inadequate sleep are key contributors to obesity and related disease risks [1, 11–15]. Diets low in polyunsaturated fats and poor adherence to healthy patterns may raise risks for neurological disorders [14]. Physical inactivity and sedentary behaviors drive energy imbalances, facilitate fat accumulation, and further metabolic decline [12, 13]. Additionally, sleep deprivation is strongly associated with obesity risk, and adequate sleep is recognized as protective [1, 15]. Sleep, another fundamental lifestyle factor, further intersects with obesity risk. Sleep duration has a paradoxical relationship with weight, influencing obesity risk despite theoretical energy expenditure [16]. Short sleep often leads to greater caloric intake and changes in diet quality and physical activity, driving weight gain [17].

Inflammation within adipose tissue (AT) is a defining molecular feature of obesity. Various studies highlighted the orchestrating role of AT inflammation in this context. The AT experiences increased infiltration of macrophages, predominantly exhibiting a pro-inflammatory M1 activation rather than the anti-inflammatory M2 phenotype. This shift leads to the secretion of high levels of pro-inflammatory cytokines, contributing to chronic low-grade inflammation (meta-inflammation) and impairing insulin signaling. The mechanisms driving macrophage accumulation in AT during obesity remain unclear, though adipocyte death and hypoxia are suspected contributors. Several intracellular pathways have been identified that may promote the pro-inflammatory activation of macrophages in AT [18].

Given this background, this narrative review explores the inflammatory milieu of adipose tissue in obesity, a key pathological axis linking excess fat accumulation to various health consequences, including metabolic syndrome, cardiovascular risk, and impaired glucose regulation. Additionally, does adipocyte dysfunction drive inflammatory and oxidative pathways that mediate obesity-related complications, mainly cardiometabolic, oncologic, and mental health implications?

2. Methods

2.1. Review Design and Rationale

This review employed a narrative synthesis approach to examine the roles of inflammation and oxidative stress in the pathophysiology of obesity. A comprehensive literature search strategy was implemented to ensure inclusion of all relevant publications.

2.2. Literature Search Strategy

Electronic databases, including PubMed and Google Scholar, were systematically searched up to the most recent date of access. The search strategy combined controlled vocabulary and free-text keywords, including “obesity,” “inflammation,” “oxidative stress,” “adipose tissue,” “cytokines,” “reactive oxygen species,” and “metabolic syndrome.” Boolean operators (AND, OR) were applied to refine results and identify studies addressing mechanistic, clinical, and epidemiological aspects of the topic.

2.3. Study Inclusion/Exclusion Criteria

The search was not limited by study design, allowing inclusion of experimental, clinical, and observational studies, as well as systematic reviews and meta-analyses that offer integrative perspectives. Manuscripts were screened for relevance based on titles and abstracts, with full texts reviewed as needed to confirm eligibility. Priority was assigned to peer-reviewed, English-language articles that provided insights into molecular pathways, biomarkers, and clinical implications of inflammation and oxidative stress in obesity. Reference lists of key articles were also manually reviewed to identify additional sources. However, literature that did not meet the aforementioned criteria was excluded from the current study.

2.4. Data Extraction Process

Data extraction prioritized the identification of recurring themes and mechanistic explanations. Evidence linking inflammatory mediators and oxidative stress markers to obesity-related outcomes was included. Studies examining therapeutic interventions or lifestyle modifications influencing these pathways were also considered.

2.5. Evidence Synthesis

The findings were narratively synthesized to provide a comprehensive overview of current knowledge. This process highlighted areas of present understanding and identified gaps requiring further investigation. The synthesis integrated diverse evidence, emphasizing the biological and clinical significance of inflammation and oxidative stress in obesity.

3. Results

3.1. Pathophysiological Landscape of Obesity

Diving deeper into the drivers of obesity, genetic, environmental, and psychosocial factors interact in complex ways to affect food intake and energy expenditure. While socioeconomic and ecological conditions shape patterns that cannot be addressed at the molecular level, identifying specific genes and molecules linked to obesity’s susceptibility reveals underlying pathophysiological mechanisms that can be targeted for intervention [19]. Studies on twins and families have estimated the rate of BMI heritability to be fairly high, accounting for 40–70% [20, 21]. Large-scale genome-wide association studies have identified over 300 loci containing common variants in the general population significantly associated with obesity traits [22]. The impact of these genetic loci on obesity risk is relatively minor, accounting for less than 5% of BMI variation [23].

Genetic and environmental factors interact to shape obesity risks, with ongoing research into epigenetics and rare genetic variants. Monogenic obesity studies underscore the central role of brain-regulated appetite and body weight, highlighting key genes and the complex regulation among the central nervous system, adipose tissue, and other organs [19].

Inflammatory changes in adipose tissue contribute directly to obesity-related diseases [24]. Expanded immune cell populations drive systemic inflammation, elevating markers such as CRP and IL-6, particularly when fat accumulates in specific body regions [25, 26]. Inflammation plays a vital role in mediating cardiovascular risk among obese individuals. Increased levels of hs-CRP and infiltration of inflammatory immune cells in visceral adipose tissue are strongly associated with higher BMI and greater risk of weight-related complications [27].

High soluble suppression of tumorigenicity-2 (sST2) is a poor-prognosis marker in chronic inflammation. Elevated levels of ST2 and its ligand IL-33 are found in the AT of obese individuals. Studies reported that circulating sST2 correlates with liver function and lipid metabolism biomarkers. Moreover, sST2 levels decrease significantly after successful bariatric surgery, especially in diabetic patients [28]. The presence of pro-inflammatory mediators in AT exacerbates obesity-related issues and metabolic syndrome, leading to conditions like hyperlipidemia, hyperglycemia, and insulin resistance (IR). Elevated TNF-α levels hinder insulin’s ability to facilitate nutrient uptake by blocking glucose transporter type 4

Table 1: Inflammatory mediators, oxidative stress molecules, and key pathways in obesity

Category	Examples	Roles in obesity
Cytokines	TNF-α, IL-6, IL-1β, MCP-1, CRP [25, 26, 29–34]	Promote chronic low-grade inflammation by activating the immune response.
Adipokines	Leptin, resistin, and adiponectin (↓) [31, 35–40]	Dysregulated adipokine secretion contributes to insulin resistance and metabolic dysfunction.
ROS	Mitochondrial electron transport chain, NADPH oxidase, xanthine oxidase, ER stress, peroxisomal β-oxidation [41]	Excess ROS production leads to oxidative damage of lipids, proteins, and DNA. It also amplifies inflammatory signaling.
RNS	Uncoupled nitric oxide synthase (NOS): mainly nitric oxide and peroxynitrite.	The same as ROS.
Key signaling pathways	NF-κB, JNK, NLRP3 inflammasome, Toll-like receptors (TLRs), mitochondrial dysfunction, ER stress [42, 43]	Central regulators of inflammatory and oxidative responses mediate adipose tissue dysfunction, insulin resistance, and systemic metabolic derangements.

TNF-α, tumor necrosis factor alpha; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; CRP, C-reactive protein; ROS, reactive oxygen species; RNS, reactive nitrogen species; NOS, nitric oxide synthase; NF-κB, nuclear factor kappa B; JNK, c-Jun N-terminal kinase; NLRP3, nucleotide-binding domain, leucine-rich repeat, pyrin domain-containing 3 inflammasome; TLRs, Toll-like receptors.

translocation in skeletal muscle cells and disrupting lipid droplet formation and triglyceride (TG) synthesis in adipocytes [29].

The metabolic syndrome (MetS), which is defined as a clustering of abdominal obesity, dyslipidemia, hyperglycemia, and hypertension, is a significant public health challenge. The average prevalence of the MetS is 31% which is associated with a two-fold increase in the risk of coronary heart disease, cerebrovascular disease, and a 1.5-fold increase in the risk of all-cause mortality [44]. In the European Prospective Investigation into Cancer and Nutrition (EPIC-CVD) study, only 20% of new CVD cases among normal-weight participants had MetS at baseline, compared with 52% among overweight participants and 76% among obese participants [45].

Lipid abnormalities in obese patients include elevated serum triglyceride (TG), very low-density lipoprotein (VLDL), apolipoprotein B, and non-high-density lipoprotein cholesterol (non-HDL-C). Increased hepatic VLDL production and reduced clearance of TG-rich lipoproteins contribute to elevated serum TG levels. High serum TG is typically associated with low HDL cholesterol levels. Low-density lipoprotein cholesterol (LDL-C) levels are often normal or slightly elevated, while small, dense LDL particles are increased [46]. Moreover, obesity increases the risk of ischemic heart disease (IHD) partly due to higher levels of non-fasting remnant LDL-C, as well as elevated blood pressure (BP) [47]. In individuals with obesity, the lipid profile is atherogenic, characterized by elevated triglycerides (TGs), low high-density lipoprotein cholesterol (HDL-C), and small, dense LDL-C particles. Increased visceral fat correlates with IR, often leading to MetS [35].

3.2. Adipocyte Dysfunction: The Nexus of Inflammation in Obesity

Adipose tissue plays a crucial role in regulating energy balance and glucose levels. White adipose tissue (WAT) primarily stores energy in the form of triglycerides. It also manages their mobilization and distribution. Additionally, WAT functions as an endocrine organ by producing bioactive factors known as adipokines. These influence various metabolic pathways across different organs. Brown adipose tissue (BAT) plays a pivotal role in thermogenesis. It converts chemical energy into heat through high levels of uncoupling protein 1 (UCP1). This process prevents hypothermia and combats obesity by burning lipids. There is also a subtype of WAT known as beige or brite fat. Beige fat can express UCP1 in response to cold exposure or to β3-adrenoceptor agonists that simulate cold stress [36]. Adipose tissue primarily serves as an energy reservoir, storing excess energy as TGs. When the body requires energy, adipocytes (fat cells) release fatty acids into circulation via lipolysis. This mobilization is crucial during periods of fasting or increased physical activity, when the body needs to utilize stored energy [48].

Beyond its role in energy storage, adipose tissue acts as an endocrine organ. Adipocytokines are hormones produced by AT that play a key role in signaling organs to maintain metabolic balance. Their dysfunction is linked to various metabolic diseases. Key adipocytokines include resistin, Leptin, and adiponectin, which are important for assessing AT dysfunction in obesity [35]. Elevated levels of resistin are associated with an increased risk of type 2 diabetes mellitus (T2D), higher inflammatory markers, and atherosclerosis. While Leptin initially has a protective role against obesity, its resistance, common in obese individuals, negates this effect and contributes to IR and CVDs. In contrast, adiponectin is viewed as a protective hormone against T2D, atherosclerosis, and CVD [37].

Adipose tissue is not merely composed of adipocytes (fat cells); it also includes a variety of other cell types, such as stromal vascular cells, immune cells, endothelial cells, and nerve cells. This diverse cellular composition allows AT to perform multiple functions beyond fat storage. The interaction between these different cell types facilitates communication within the tissue and with other organs through various signaling mechanisms [49].

Obesity is characterized by a chronic, low-grade inflammatory response that differs from that induced by tissue injury or infection. The inflammation associated with obesity arises primarily from the immune response to excess metabolites produced by accumulated adipose tissue. Macrophages migrate from the bloodstream to adipose tissue, where they differentiate into pro-inflammatory M1 macrophages. The increase in M1 phenotype is a key factor in obesity-related inflammation. These cells secrete cytokines such as TNF-α, IL-1β, and IL-6, as well as ROS, contributing to various metabolic disorders [30].

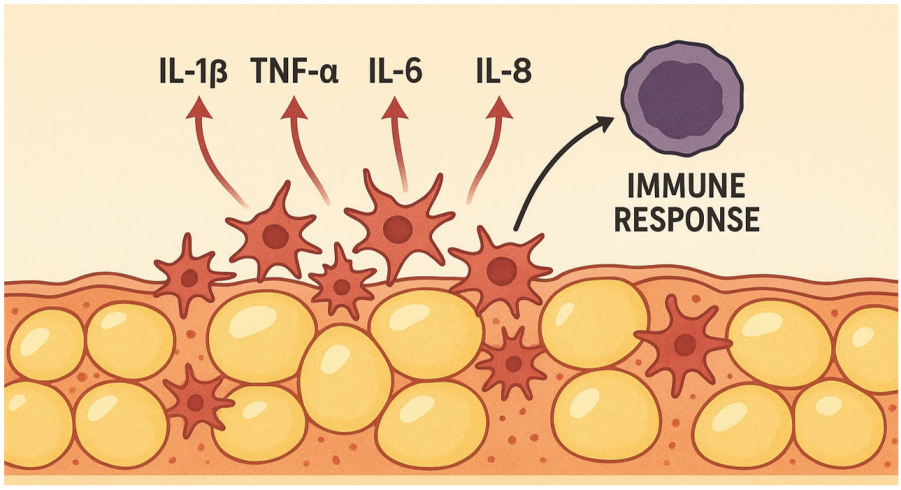

Figure 1: Adipose tissue inflammation in obesity.
During inflammation, adipocytes are the predominant source of pro-inflammatory cytokines, including IL-1β, TNF-α, and IL-6, thereby triggering immune responses that generate oxidative stress molecules. This cascade contributes to the onset of progression of various health complications. This figure has been generated by the AI tool (ChatGPT).

White (WAT) and brown (BAT) adipose tissues function as endocrine organs, in addition to their roles in energy storage and thermoregulation. They interact with other organs to regulate metabolism by releasing adipokines and cytokines, which include signaling lipids (adipokines) and exosomal microRNAs (miRNAs) [50]. WAT secretes various active adipokines, including adiponectin, IL-1, IL-6, IL-8, IFN-γ, TNF-α, Leptin, apelin, chemerin, and resistin. These adipokines regulate metabolic homeostasis and modulate immune responses [31]. Adipocytes mainly produce Leptin, which is closely linked to overall body obesity. While other tissues, such as the stomach, brain, skeletal muscles, and bones, can produce smaller amounts of Leptin, its primary source remains fat cells. As a pro-inflammatory adipokine, Leptin is essential in regulating the immune response [38]. A prospective study involving older adults found a positive correlation between serum Leptin concentrations and muscle weakness, though it does not directly correlate with skeletal muscle mass [51]. A recent study found that plasma Leptin levels in older women are positively associated with BMI and negatively associated with skeletal muscle index (SMI), a measure of sarcopenia [52]. However, adiponectin is primarily secreted by adipose tissue but is also produced in other tissues, including skeletal muscle. This anti-inflammatory adipokine enhances insulin sensitivity in both obese animals and humans [39].

Resistin is a pro-inflammatory adipokine produced by immune cells within AT. It plays a substantial role in interconnecting visceral obesity (VO) with type 2 diabetes mellitus [53]. The resistin/IGF-1 (insulin-like growth factor 1) ratio declines with age, and this decline is associated with reduced muscle strength. Additionally, it suppresses myogenesis, particularly in aging skeletal muscle [32, 54]. Tumor necrosis factor alpha (TNF-α) is a cytokine produced by adipocytes and inflammatory cells as a response to chronic inflammation. It plays a significant role in the pathophysiology of various metabolic disorders [40]. The TNF-α is primarily synthesized in adipocytes and various peripheral tissues. It promotes tissue-specific inflammation by increasing ROS production and activating multiple transcriptional pathways. Elevated TNF-α levels contribute to the development of IR in both adipocytes and peripheral tissues. This occurs through impairment of insulin signaling mechanisms, specifically via serine phosphorylation, ultimately leading to the onset of T2D [33].

Interleukin-6 (IL-6) is another main player in the inflammatory immune response. It is produced by various cell types, including macrophages, monocytes, and lymphocytes, particularly at sites of inflammation. It primarily stimulates the production of acute-phase proteins by hepatocytes in the liver, which are essential components of the acute-phase response. The latter is a systemic reaction to inflammation or injury characterized by changes in plasma protein levels [32]. Upon activation during inflammatory processes, IL-6 binds its receptor on target cells, initiating signaling pathways that lead to the transcription of genes encoding acute-phase proteins such as CRP, fibrinogen, and serum amyloid A. The elevation of these proteins serves various functions: enhancing the opsonization of pathogens, promoting clot formation, and modulating immune responses [34].

3.3. The Crosstalk Between Obesity-Induced Inflammation and Oxidative Stress

Inflammation is a biological response to tissue injury. It is characterized by the accumulation of immune cells and fluid in affected areas, which helps protect tissues from further damage. Inflammation can be acute or chronic. Acute inflammation typically arises as a short-term response to immediate injury or infection. Chronic inflammation may develop if the acute phase fails to resolve, or it may emerge independently due to persistent irritants [55]. Obesity is associated with chronic systemic inflammation. This can result in IR and dysfunction of pancreatic β-cells, ultimately leading to the development of T2D. This persistent inflammatory condition plays a significant role in the long-term complications associated with diabetes, such as non-alcoholic fatty liver disease (NAFLD), retinopathy, CVDs, and nephropathy. Furthermore, this inflammation may explain the links between T2D and other health issues, including Alzheimer's disease, polycystic ovarian syndrome, gout, and rheumatoid arthritis [56].

Reactive oxygen and nitrogen species (RONS) are generated through various internal biological processes and external factors. The detrimental effects of RONS are counteracted by the body's

antioxidant defense mechanism [57]. These molecules arise from both endogenous and exogenous sources. Endogenous ROS is produced during inflammation, immune cell activation, intense exercise, ischemia, mental stress, cancer, infections, and aging. Exogenous sources include environmental pollutants, alcohol, smoking, certain medications (e.g., tacrolimus and cyclosporine), heavy metals, radiation, cooking, and solvents. Once inside the body, these molecules are converted into ROS. Consequently, these compounds damage cellular macromolecules (proteins, lipids, and nucleic acids), contributing to the development and progression of diseases such as diabetes, CVDs, atherosclerosis, liver diseases, and cancers [58].

At the molecular level, ROS primarily originate from the mitochondrial electron transport chain (ETC) that generates superoxide anions. Superoxide reacts with iron-containing proteins to form hydrogen peroxide (H2O2), which accumulates in cells. This process is linked to metabolic imbalances associated with nutrient stress and IR. ROS includes several chemical types, such as nitric oxide, peroxynitrite, hypochlorous acid, singlet oxygen, and hydroxyl radicals. The diverse effects of ROS result from different cellular environments that influence physiological and pathological outcomes [41]. High ROS levels modify cellular proteins and lipids, leading to cellular dysfunction impacting energy metabolism, cell signaling, transport mechanisms, immune activation, and inflammation. Nutritional stress from high-fat and carbohydrate diets increases oxidative stress. This is reflected by higher lipid peroxidation, increased protein carbonylation, and lower antioxidant levels [57].

TNF-α, tumor necrosis factor-alpha; IL-6, interleukin-6; IL-1β, interleukin-1 beta; MCP-1, monocyte chemoattractant protein-1 (CCL2); CRP, C-reactive protein; ROS, reactive oxygen species; RNS, reactive nitrogen species; NOS, nitric oxide synthase; NADP(H), nicotinamide adenine dinucleotide phosphate (oxidized NADP+/reduced NADPH); ER, endoplasmic reticulum; ETC, electron transport chain; NF-κB, nuclear factor kappa B; JNK, c-Jun N-terminal kinase; NLRP3, NLR family pyrin domain-containing 3; TLRs, toll-like receptors; ↓, decreased.

In obesity, chronic oxidative stress and inflammation contribute to IR, metabolic dysfunction, diabetes, and CVDs by disrupting insulin signaling and immune responses. Conversely, exercise can mitigate oxidative stress and enhance metabolic and inflammatory health [59]. Oxidative stress may serve both as a consequence of obesity and as a contributing factor to its onset. Research indicates a significant correlation between oxidative stress and inflammatory processes associated with obesity. Adipose tissue plays a central role in this association by secreting pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6. These cytokines are known to stimulate ROS production, which can further exacerbate oxidative stress [60]. Studies indicated that young patients with MetS exhibit elevated oxidative stress levels and reduced superoxide dismutase activity, highlighting the role of impaired antioxidant defenses in this oxidative environment [61]. Additionally, moderate caloric restriction over 8 weeks in obese patients led to weight loss, enhanced antioxidant defenses, reduced oxidative stress markers, improved glucose tolerance, and decreased IR [62].

Obesity leads to elevated plasma-free fatty acid (FFA) levels and excessive fat accumulation in WAT. Elevated plasma FFA levels can inhibit the translocation of adenine nucleotides and enhance the production of superoxide radicals ($O_2 \cdot^-$) within the mitochondrial electron transport chain. Additionally, FFAs activate protein kinase C (PKC), which, in turn, stimulates the Nicotinamide Adenine Dinucleotide Phosphate (NADPH) oxidase (NOX) pathway in vascular cells, leading to ROS generation. Conjugated fatty acids are particularly prone to oxidation, thus promoting the formation of oxidative stress by-products. In obese individuals, there is a notable increase in 4-hydroxynonenal (4-HNE), a marker of lipid peroxidation, indicating greater lipid susceptibility to oxidative damage. The elevated lipid concentration in obesity also provides a larger target for ROS modification [63].

3.4. The Interplay Between Immune Cells and Inflammation

In addition to adipocytes, adipose tissue contains a network of immune cells that collaborate to regulate metabolism and organ function. In recent years, the significance of these immune cells has increased as they have been recognized for their central role in coordinating immunity, metabolic processes, and tissue health [64]. Macrophages are essential components of the innate immune system, playing key roles in maintaining homeostasis and responding to disease. These white blood cells (WBCs) derive from monocytes and can adapt to different forms in response to environmental signals. In adipose tissue, they are primarily categorized into two phenotypes: M1 (pro-inflammatory) and M2 (anti-inflammatory). In obesity, macrophages are often polarized toward a pro-inflammatory M1 phenotype. When stimulated by lipopolysaccharides and saturated fatty acids, they release pro-inflammatory cytokines, mainly TNF-α, IL-6, IL-12, and IL-1β. This process contr

T cells are another subset of primary immune cells in visceral adipose tissue (VAT). In obesity, these cells accumulate, leading to inflammation characterized by the release of pro-inflammatory cytokines and chemokines [65]. Changes in T cell components in inflamed AT correlate with the level of obesity-related inflammation [66]. T cells are classified into CD8+ T cells, which recognize antigens presented by MHC I, and CD4+ T cells, which interact with antigens presented by MHC II [67]. In obesity, the balance between proinflammatory and anti-inflammatory T cells shifts. The increase in proinflammatory T cells, along with the production of proinflammatory cytokines, contributes to AT inflammation [65].

B cells, on the other hand, infiltrate VAT and undergo functional and phenotypic changes due to diet-induced obesity. These cells contribute to insulin resistance by presenting antigens to T cells, releasing inflammatory cytokines, and producing harmful antibodies. Targeting B cells offers a promising strategy for treating obesity-related IR and may help prevent T2D [68]. Over the past few decades, neutrophils have been recognized for their vital role in inflammation. They are persistently recruited to inflamed tissues, where they contribute to the inflammatory process by releasing serine proteases, forming neutrophil extracellular traps (NETs), and activating other immune cells [69].

3.5. Health Implications of Obesity

Obesity directly increases the risk of cardiovascular disorders such as dyslipidemia, T2D, and hypertension [70]. It independently increases the risk of CVDs, including coronary artery disease (CAD), heart failure (HF), and atrial fibrillation (AF) [71]. Severe obesity significantly burdens cardiovascular risk factors, including elevated BP, MetS, diabetes mellitus, lipid abnormalities, and inflammation. These conditions negatively impact cardiac structure and function. Recent studies indicate that the relationship between obesity and cardiometabolic risk factors can be observed even in early life stages [72]. Altogether, the severity of obesity and its related disorders is consistent with the increase in the prevalence of the aforementioned cardiovascular diseases [73].

Abdominal obesity is a significant, modifiable risk factor for atrial fibrillation in non-obese Asian individuals. Reducing abdominal

obesity could substantially lower its overall incidence in this population [74]. Diets rich in carbohydrates and alcohol can increase blood triglyceride levels, a risk factor for atherosclerosis [75]. High dietary fat and carbohydrate intake may acutely activate peripheral α1- and β-adrenergic receptors, leading to increased sympathetic activity and hypertension [76]. Epidemiological evidence suggests that type 2 diabetes mellitus and obesity are interconnected issues that are increasingly prevalent worldwide. Obesity contributes to IR, which is a significant factor in the development of T2D, potentially accounting for up to 80% of the risk associated with this condition [77]. Most individuals with T2D are overweight or obese, making weight loss a recommended treatment approach for managing the aforementioned condition [78].

Obesity has been linked to several common types of cancers, including breast, colorectal, esophageal, kidney, gallbladder, uterine, pancreatic, and liver cancer [79]. Obesity is not only associated with an increased incidence of cancer recurrence but may also increase the risk of cancer-related deaths and may influence treatment options [80]. Research exploring the relationship between obesity and thyroid cancer indicates that a five-point increase in BMI increases the risk of thyroid cancer by 30%. In comparison, a 0.1-point increase in waist-to-hip ratio increases the risk by 14% [81]. The prevalence of overweight and obesity has surged significantly in both developing and developed nations, reaching pandemic levels where 60-70% of adults in industrialized countries are affected. This issue is more pronounced among females and in urban populations [79].

The relationship between obesity and mental health can be described as a bidirectional impact where each condition can exacerbate the other. Although the mental health complications may not directly reflect the main scope of the current review, they should be highlighted as one of the primary complications developed by obesity. Therefore, we wanted to shed light on the psychological consequences as well. Individuals with obesity face significant risks for various mental health disorders due to factors such as societal stigma, emotional distress related to body image issues, and the direct effects of disordered eating behaviours. Therefore, addressing both physical and psychological aspects through comprehensive treatment approaches is essential for improving overall well-being in obese individuals [82].

The psychological effects of obesity are closely linked to emotional and behavioral factors. Stress and emotional distress often lead individuals to use food as a coping mechanism, resulting in emotional eating and subsequent weight gain. This cycle not only increases the risk of obesity but also intensifies feelings of guilt and shame, negatively affecting mental health. The stigma associated with obesity can result in social isolation, low self-esteem, and body image issues, which may lead to depressive symptoms and anxiety. This isolation creates a cycle where lack of social support and increased loneliness hinder the ability to adopt healthier behaviors or seek assistance. Body image dissatisfaction involving societal pressures to meet certain body standards can lead to negative self-image and low self-esteem in individuals with obesity. This may result in mood disorders, anxiety, and eating disorders. Additionally, childhood experiences and trauma can influence eating patterns and self-esteem, impacting long-term weight [83].

Obesity and eating disorders are each associated with severe physical and mental health consequences in obese individuals. Moreover, obesity can contribute to eating disorder behaviours and vice versa [84]. Binge eating disorder and bulimia nervosa are the most commonly studied eating disorders in individuals with obesity. The first condition involves recurrent binge eating episodes occurring at least once a week for three months, accompanied by significant distress. To meet the criteria, individuals must exhibit at least three of the following five behaviors: eating rapidly, consuming large amounts until uncomfortably full; eating without physical hunger; eating alone due to embarrassment about food intake; and feeling disgusted, depressed, or guilty after binge episodes [85]. Bulimia nervosa is marked by an excessive focus on body weight and shape, episodes of binge eating, and unhealthy behaviors to avoid weight gain, such as self-induced vomiting, laxative misuse, fasting, or excessive exercise [3]. Compared to normal weight, obesity in grades 2 and 3 significantly increased all-cause mortality; however, grade 1 obese individuals did not show a similar association. This indicates that higher BMI levels are primarily responsible for the increased mortality rate linked to obesity [86].

4. Discussion

The evidence in this review highlights how inflammation and oxidative stress drive obesity. Adipose tissue expansion triggers immune cell infiltration, especially by macrophages. These cells secrete pro-inflammatory cytokines (TNF-α, IL-6, and IL-1β) [42]. The cytokines activate signaling pathways (NF-κB and JNK), leading to chronic low-grade inflammation and metabolic dysfunction. Excess nutrient intake and enlarged adipocytes cause mitochondrial dysfunction, ER stress, and activation of NADPH oxidase, leading to increased reactive oxygen and nitrogen species (ROS/RNS). Together, these factors cause insulin resistance, endothelial dysfunction, and wide metabolic disturbances. Thus, inflammation and oxidative stress are not merely features but key mechanisms in the development and progression of obesity [43].

Despite the central mechanistic role of inflammation and oxidative stress, clinical observations remain controversial. For instance, the "obesity paradox" in cardiovascular disease (CVD) shows that overweight or mildly obese people may survive longer than leaner individuals with similar comorbidities. This paradox challenges the notion of a simple link between body fat and risk and raises questions about the value of body mass index (BMI) relative to metabolic health [87]. People with metabolically healthy obesity (MHO) have lower levels of inflammation and oxidative stress than those with metabolically unhealthy obesity, even when their BMI is the same. These findings complicate risk assessment and suggest that inflammation and oxidative stress may be better markers of cardiometabolic risk than body measurements alone [88].

Building on these complexities, it is important to note that although numerous studies support the involvement of inflammatory and oxidative pathways, several gaps remain. First, heterogeneity in study populations, methodologies, and biomarker selection limits the comparability of findings. Second, the directionality of causality between inflammation, oxidative stress, and obesity is unclear, as available evidence suggests these processes may reinforce each other in a complex, bidirectional manner rather than follow a simple cause-and-effect sequence [1]. Third, data on the role of specific adipokines, such as adiponectin, are inconsistent, with evidence supporting both protective and detrimental effects depending on the context. Additionally, the contribution of tissue-specific oxidative stress across hepatic, adipose, and vascular compartments [89].

Given these ongoing challenges, translating these insights into effective therapeutic strategies remains limited. Pharmacological interventions, such as TNF-α inhibitors or antioxidant supplementation, have produced only inconsistent or modest clinical benefits [90]. Lifestyle changes, including diet and physical activity, are most effective at reducing inflammation and oxidative stress [91].

However, adherence and sustainability are common problems. This gap between mechanistic understanding and clinical application shows the need for precision medicine using biomarker profiling, patient stratification, and targeted therapies. Bridging the translational gap is essential for meaningful clinical outcomes and targeted therapies.

4.1. Limitations

This review uses a narrative approach and does not meet the strict standards of systematic reviews. As a result, the process for choosing studies may be incomplete, and some important publications may have been missed even though searches were done in PubMed and Google Scholar. Using a narrative method adds subjectivity in how findings are understood and combined. Also, it is hard to compare results because the studies differ significantly in design, participants, and biomarker tests. In many areas, such as those on tissue-specific oxidative stress or long-term human data, the evidence is limited or mixed, which weakens the strength and generality of the conclusions. These limits highlight the need for more comprehensive systematic reviews, meta-analyses, and stronger human studies to confirm and expand the ideas discussed here.

5. Conclusions

Obesity remains a significant global public health challenge, with prevalence increasing across various populations and age groups. A key factor in its pathophysiology is adipose tissue dysfunction. In addition to its role in energy storage, adipose tissue acts as a dynamic endocrine organ. When dysregulated, it becomes a major source of pro-inflammatory cytokines and reactive oxygen species, triggering a cascade of immunometabolic disturbances. Chronic low-grade inflammation and oxidative stress not only worsen metabolic imbalance but also contribute to a range of obesity-related complications, such as insulin resistance, cardiovascular disease, and certain cancers. Future research should prioritize identifying biomarkers of inflammation and oxidative stress that predict cardiometabolic outcomes. Furthermore, studies should assess whether interventions targeting these pathways improve clinical outcomes beyond the benefits of weight loss alone. Addressing obesity requires more than clinical management; it necessitates proactive, population-level interventions grounded in education and awareness. Clarifying the biological mechanisms and systemic effects of adipose tissue dysfunction enables public health initiatives to better inform individuals about the often-silent progression of obesity-related diseases. Disseminating evidence-based information empowers communities to make informed decisions and adopt healthier lifestyles, thereby enhancing the long-term health of individuals and society.

Conflicts of Interest

The authors declare no conflicts of interest.

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Large Language Model

During the preparation of this work, the authors used the AI-assisted tool Grammarly (Grammarly Inc.) to help identify and suggest corrections for grammar, spelling, and clarity. After applying suggested changes, the authors carefully reviewed and edited the text, retaining full responsibility for the final content of the published article. Additionally, the authors used ChatGPT to generate **(Figure 1)**. The authors thoroughly reviewed the generated content to ensure it accurately represents the conceptual intent and scientific ideas originally envisioned.

Authors Contribution

MK conducted the comprehensive literature search, selected relevant studies for inclusion, and drafted the original draft. AH conceived the idea for the review, defined its scope and objectives, revised the manuscript for intellectual content, clarity, and coherence, and supervised the project.

Data Availability

This review article was prepared based on previously published studies. No new data were created or analyzed in this study. The datasets supporting the conclusions are available in the cited sources. The search strategy and inclusion criteria are described in the Methods section to ensure reproducibility.

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